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## **Variable interpretation of the Dystonia Consensus Classification items compromises its solidity**

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## VIEWPOINT

"Everything must be made as simple as possible. But not simpler."

- Albert Einstein

The improving knowledge on dystonia etiology and associated phenomenology led to the revision of its definition and classification, which was published in 2013<sup>1,2</sup>. This consensus-based classification aimed to facilitate diagnosis, diagnostic testing and treatment, and to assist in the development of research strategies.<sup>1</sup>

The classification system includes two axes: the first axis focuses on the clinical manifestations of dystonia, the second axis on etiology.<sup>1</sup> Once a patient has been phenomenologically classified according to the first Axis (Table 1) a dystonia syndrome can be defined.<sup>1</sup> To assist clinicians in defining a specific dystonia syndrome, Fung and colleagues listed 27 dystonia syndromes, supplemented with lists of potential etiologies for 16 of them.<sup>3</sup>

The 2013 Dystonia Consensus Classification has been built thanks to the effort of world experts in dystonia and proposed to address some issues raised by the former classification. It has a solid structure, and great attention has been posed in dissecting and representing the multiple facets of this complex disorder. Altogether it definitely represents a step forward in the field.

Any clinical classification, however, will only be as solid as the capacity of clinicians to interpret its items and translate them into the clinical evaluation in a reproducible manner. At first sight, the criteria of the dystonia classification seem to be clear and straightforward. However, in our multicenter experience, applying the criteria in clinical practice often led to discussion among colleagues, because the terms of the classification were interpreted in different ways. Such variability in interpretation carries the risk of different diagnostic and treatment strategies being employed, and may well hamper the search for phenotype-genotype correlations.

To trigger discussion on the terms of classification we use a clinical example. A 10-year-old boy, born at 36 weeks with mild perinatal asphyxia, and with delayed motor milestones, presented at the age of 4 with episodes of 'jerky movements' of both arms triggered by emotion or stress. Later he developed continuous abnormal 'twisting' movements that gradually progressed over the first few years, to stabilize later on. He often sits in a twisted posture, his torso and head turned aside. Co-occurrent problems are mental retardation, autism and asthma. On neurological examination ocular apraxia was noted with abnormal saccadic eye movements. He had cervical and truncal dystonia with myoclonus of both arms and action-induced dystonic posturing of both feet and both hands. For this case, two experienced clinicians independently assessed all Axis I items of the dystonia classification<sup>1</sup> and defined the dystonia syndrome,<sup>3</sup> based on a written vignette. Divergent answers were given with regard to age at onset ('infancy' and 'childhood'), disease course ('static' and 'progressive') and associated features ('mental retardation' versus 'mental retardation, autism and asthma').

As a pilot project, to further explore the possible variability in the interpretation of the classification terms by different clinicians, 55 other written case vignettes of patients with dystonia with a suspected genetic cause (46% male, age 1-73 years)<sup>4</sup> were assessed in the same way. Each description (including medical/family history, medications, neurological examination, and brain MRI report) was anonymously assessed by two of eight international movement disorders experts, who independently classified the phenomenological features according to the dystonia classification (Axis

1).1 We used written case reports deliberately, because these might give rise to less variability than video examinations, 5•8 as some choices regarding the clinical characterization have already been made by the author of the vignette. Interestingly, a 100% agreement for all Axis I items was observed in only 9/56 cases (16.1 %) (for specification per item see Supplement 1-2).

### **How the classification criteria may lead to ambiguity**

Although several factors may have contributed to non-agreement, a variable interpretation of clinical information among clinicians has possibly been driven by some ambiguity in the classification items themselves. To clarify this, we will discuss some clinical examples for each Axis I item.

**Age at onset.** Abnormal motor development in children presenting before the onset of frank dystonic symptoms, generated divergent answers regarding 'age at onset' in several cases. Similarly, in combined syndromes, the presence of co-occurring symptoms preceding the onset of dystonic symptoms led to uncertainty concerning the real onset of the disorder.

Lastly, different interpretations of the age at onset could be explained by dystonic jerks and dystonic posturing starting at different ages.

**Body distribution.** A patient with myoclonus-dystonia with dystonia in the neck and myoclonus in the limbs could be classified as having focal dystonia or generalized dystonia, depending on whether the accent was put on the dystonic symptom or on the whole manifestation of the syndrome. In case of paroxysmal symptoms, when clinical examination is typically unrevealing, it turned out to be challenging to define the item 'body distribution', also considering that the descriptions by the patient or caregivers are often inaccurate and that there might be a considerable variability between the episodes described.

**Disease course.** Two patients had progressive dystonic jerks and stable dystonic posturing, which in both cases gave rise to divergent answers regarding 'disease course'. Another illustrative case concerned a young patient with progressive dystonic symptoms and an abnormal motor development that had stabilized. This was interpreted by one clinician as a progressive and by the other clinician as a static course of the dystonia.

**Variability.** In multifocal or generalized dystonia, the item 'variability' led to

different interpretations. For example, dystonic movements could be action-specific in one part of the body but persistent elsewhere. Moreover, it can be unclear whether this item refers to symptoms (history) or signs (examination). While clinicians may tend to rely purely on clinical examination, for assessing "variability" the evaluation of history may be required: for example in case of diurnal fluctuations. Another example includes the phenomenon when only persistent dystonia is seen in the office, while the patient reports action-specific dystonia in particular situations.

**Isolated or combined.** For paroxysmal dystonia, the item 'isolated or combined' could be difficult to classify, for the same reasons as described for the item 'body distribution'. Another source of confusion might be the interpretation of jerky movements. Despite the fact that every clinician had access to the same description of the phenomenology, it appeared that some clinicians made their own interpretation of co-occurring jerky movements, based on the complete clinical picture and pattern recognition, reflecting a common dilemma in clinical practice. For instance, jerky movements can be classified as dystonic jerks without any co-

occurring movement disorder by one clinician and as chorea or even myoclonus by another, leading to a different "isolated" or "combined" definition.

It should be noted that some of the above-mentioned classification items are interconnected; for example, if jerky movements are interpreted by one rater as myoclonus and by the other as dystonic jerks, the answers will not only differ for the item 'isolated or combined', but often for other items too, such as 'body distribution', 'age at onset' and 'disease course'. Furthermore, it goes without saying that if no agreement was reached on the phenomenological classification according to Axis I, this will result in different dystonia syndromes, as the list of syndromes is based on stratification of the classification items.<sup>3</sup>

### **Can these issues be overcome?**

Our preliminary observations show how a classification system, when used to cover all complexities of the real world, can result in ambiguities in interpretation. The few examples presented here probably do not cover all the potential ambiguities that might rise in daily practice. However, we believe that our exploratory observations can be food for thought and the basis to propose some improvements.

Theoretically, more stringent Axis I criteria might improve some of the factors leading to ambiguity. For example, co-existent jerks and dystonia in the same body region may be defined as dystonic movements rather than as myoclonus.<sup>9</sup> Similarly, specific instructions might be added on how to apply the criteria, for instance for the item 'variability' it might be relevant to add whether it refers to symptoms (history) or signs (examination), and for the item 'disease course' a time frame might be added (e.g. in the past year).

On the other hand, we might consider simplifying the current dystonia classification for those items for which it is difficult to formulate strict criteria, or to give a lower level of relevance to those items that may not be essential for assembling meaningful subgroups. Particularly because considering the options for all items of the dystonia classification, there are thousands of possible independent item combinations that could be generated and not all these subgroupings may be relevant in clinical practice.<sup>10</sup>

### **Future directions**

Obviously, an appropriate clinical characterization will always heavily rely on the clinician's experience and intuition, given the nature of movement disorders. When we look at the classification of dystonia from a broader perspective, beyond possible adaptations of the classification items, we think that the variability in interpretation among clinicians can be reduced by both training programs and panel ratings. Strategies such as (web-based) training programs, analogous to the training developed for the Movement Disorder Society's Unified Parkinson's Disease Rating Scale (MDS-UPDRS)<sup>11</sup> could improve the agreement among clinicians

worldwide. Furthermore, similar to what has been suggested in the field of epilepsy,<sup>12</sup> regular team assessments by a panel of raters and consensus meetings, could reduce variability in interpretation, and form a valuable environment for continuous education and training.

Evidently, disease classification systems, and the way we use them, are continuously evolving. For dystonia, this debate dates back to 1911 when Flatau and Sterling objected to the term "dystonia" coined by Oppenheim.<sup>13,14</sup> Considering that the current classification of dystonia was established through a consensus process, we believe it is necessary to put the criteria to test, similar to what recently has been done for the clinical diagnostic criteria for Parkinson's disease.<sup>15</sup> For dystonia, the preliminary observations described in this Viewpoint can serve as a starting point, but definitely more studies with solid methodology are needed, to fuel discussion, identify weak points, and propose further improvements.

### **Authors' Roles**

Martje E. van Egmond: organization and execution of research project, assessment of clinical case descriptions, drafting manuscript; Maria Fiorella Contarino: assessment of clinical case descriptions; drafting manuscript; Coen HA. Lugtenberg: organization and execution of research project, data analysis, review and critique of manuscript; Kathryn J. Peal/ assessment of clinical case descriptions; review and critique of manuscript; Oebele F. Brouwer: assessment of clinical case descriptions; review and critique of manuscript; Victor S.C. Fung: assessment of clinical case descriptions; review and critique of manuscript; Emmanuel Roze: assessment of clinical case descriptions; review and critique of manuscript; Roy E. Stewart: performing statistical analyses, review and critique of manuscript; Michel A. Willemsen: assessment of clinical case descriptions; review and critique of manuscript; Nicole Wolf assessment of the clinical case descriptions; review and critique of manuscript; Marina A. Tijssen: conception, organization and execution of research project, review and critique of manuscript; Tom J. de Konin[J]: conception, organization and execution of research project, review and critique of manuscript.

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**Table 1.** Dystonia consensus classification (adapted from Albanese et al.<sup>1</sup>)

Axis I. Clinical characteristics of dystonia
<p><i>Age at onset</i></p> <ul style="list-style-type: none"> <li>• Infancy (birth to 2 years)</li> <li>• Childhood (3-12 years)</li> <li>• Adolescence (13-20 years)</li> <li>• Early adulthood (21-40 years)</li> <li>• Late adulthood (&gt;40 years)</li> </ul> <p><i>Body distribution</i></p> <ul style="list-style-type: none"> <li>• Focal</li> <li>• Segmental</li> <li>• Multifocal</li> <li>• Generalized (with or without leg involvement)</li> <li>• Hemidystonia</li> </ul> <p><i>Temporal pattern</i></p> <p>Disease course</p> <ul style="list-style-type: none"> <li>• Static</li> <li>• Progressive</li> </ul> <p>Variability</p> <ul style="list-style-type: none"> <li>• Persistent</li> <li>• Action-specific</li> <li>• Diurnal</li> <li>• Paroxysmal</li> </ul> <p><i>Associated features</i></p> <p>Isolated dystonia or combined with another movement disorder</p> <ul style="list-style-type: none"> <li>• Isolated dystonia</li> <li>• Combined dystonia</li> </ul> <p>Occurrence of other neurological or systemic manifestations</p> <ul style="list-style-type: none"> <li>• List of co-occurring neurological manifestations</li> </ul>



**Supplement 1.** Inter-rater agreement for the first five Axis I items of the dystonia classification and for the dystonia syndrome

	Agreement	agreement %	inter-rater agreement, kappa	95% confidence interval
<b>Items dystonia classification (Axis I)</b>				
Age at onset	46/56	82.1	0.80 <sup>b</sup>	0.69 - 0.91
Body distribution	34/56	60.7	0.45	0.27 - 0.63
Temporal pattern, disease course	44/56	78.6	0.52	0.29- 0.76
Temporal pattern, variability	47/56	83.9	0.62	0.41- 0.83
Isolated or combined	44/56	78.6	0.50	0.27 - 0.73
<b>Dystonia syndromesc</b>				
Dystonia syndrome-	31/56	55.3	0.5	0.40-0.59

• Fleiss' kappa assessing interrater agreement between two raters. Kappa categories: <0.0 poor, 0.0 to 0.2 slight, 0.21 to 0.40 fair, 0.41 to 0.60 moderate, 0.61 to 0.80 substantial, and 0.81 to 1.0 excellent.

<sup>b</sup> weighted kappa.

craters selected a dystonia syndrome out of the list of 27 dystonia syndromes from the paper of Fung et al.<sup>3</sup>

**Supplement 2.** Agreement with regard to co-occurring neurological or systemic manifestations

	Feature 1	Feature 2	Feature 3	Feature 4
Both clinicians gave an answer	<b>20</b>	<b>5</b>	<b>2</b>	<b>2</b>
<i>Agreement</i>	20	3	2	2
<i>Non-agreement</i>	0	2	0	0
One of the clinicians gave an answer	<b>15</b>	<b>15</b>	<b>5</b>	<b>1</b>
<i>Psychiatric and behavioral Problems</i>	5	1		
<i>Static cognitive impairment</i>	2	3		
<i>Cognitive decline</i>		1	1	
<i>Cranial nerves and sensory input</i>	1	1		
<i>Peripheral nerves</i>		2	1	
<i>Muscle symptoms</i>	2	1		
<i>Paroxysmal disorders</i>	2	1		
<i>Dysmorphisms/skeletal abnormalities</i>	1	1	1	
<i>Systemic disorders</i>	1	3		
<i>Miscellaneous</i>	1	1	2	1
Neither clinician gave an answer	<b>21</b>	<b>36</b>	<b>49</b>	<b>53</b>
<b>Agreement*</b>	<b>73%</b>	<b>70%</b>		

- \* Percentage of agreement was defined as the percentage of cases in which both clinicians gave an answer in the same category, plus the percentage of cases in which both clinicians agreed upon the absence of other neurological or systemic manifestations. We only calculated the percentage of agreement for those cases with one or two features mentioned, as these were considered the most relevant.